

# A practical guide to using oral Janus kinase inhibitors for atopic dermatitis from the International Eczema Council

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## Abstract

**Background** Janus kinase inhibitors (JAKi) have the potential to alter the landscape of atopic dermatitis (AD) management dramatically, owing to promising efficacy results from phase III trials and their rapid onset of action. However, JAKi are not without risk, and their use is not appropriate for all patients with AD, making this a medication class that dermatologists should understand and consider when treating patients with moderate-to-severe AD.

**Objectives** To provide a consensus expert opinion statement from the International Eczema Council (IEC) that provides a pragmatic approach to prescribing JAKi, including choosing appropriate patients and dosing, clinical and laboratory monitoring and advice about long-term use.

**Methods** An international cohort of authors from the IEC with expertise in JAKi selected topics of interest were placed into authorship groups covering 10 subsections. The groups performed topic-specific literature reviews, consulted up-to-date adverse event (AE) data, referred to product labels and provided analysis and expert opinion. The manuscript guidance and recommendations were reviewed by all authors, as well as the IEC Research Committee.

**Results** We recommend that JAKi be considered for patients with moderate-to-severe AD seeking the benefits of a rapid reduction in disease burden and itch, oral administration and the potential for flexible dosing. Baseline risk factors should be assessed prior to prescribing JAKi, including increasing age, venous thromboembolisms, malignancy, cardiovascular health, kidney/liver function, pregnancy and lactation, and immunocompetence. Patients being considered for JAKi treatment should be current on vaccinations and we provide a generalized framework for laboratory monitoring, although clinicians should consult individual product labels for recommendations as there are variations among the different JAKi. Patients who achieve disease control should be maintained on the lowest possible dose, as many of the observed AEs occurred in a dose-dependent manner. Future studies are needed in patients with AD to assess the durability and safety of continuous long-term JAKi use, combination medication regimens and the effects of flexible, episodic treatment over time.

**Conclusions** The decision to initiate JAKi treatment should be shared between the patient and provider, accounting for AD severity and personal risk–benefit assessment, including consideration of baseline health risk factors, monitoring requirements and treatment costs.

## Lay summary

Drugs called Janus kinase inhibitors ('JAKi' for short) have the potential to change how atopic dermatitis (or 'AD') is treated. Promising results from clinical trials and their ability to work quickly make JAKi a type of medication that should be considered for treating moderate-to-severe AD. There are some risks with JAKi treatment and they are not appropriate for all people with AD.

Researchers from around the world reviewed the published information on JAKi. We provide a sensible approach to prescribing these drugs. We considered three JAKi used to treat AD. Although each JAKi is different in how effective it is and what the side effects are, we have tried to provide general guidance that may be used for all JAKi.

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This guidance allows for standardization and simplification of prescribing JAKi to treat AD. However, some procedures or how often monitoring is done, are slightly different for each JAKi. Using the most current safety data, we provide recommendations that cover all JAKi.

### What is already known about this topic?

- Oral JAK inhibitors (JAKi) are highly effective, fast-onset medications used to treat moderate-to-severe atopic dermatitis (AD).
- Previous studies of JAKi have found an increased risk of adverse effects (e.g. major cardiovascular events, malignancies and infection) in people without AD.
- Appropriate patient selection for oral JAKi treatment is important.

### What does this study add?

- This consensus expert opinion statement provides a pragmatic approach to prescribing JAKi, including choosing appropriate patients and dosing, clinical and laboratory monitoring and advice about long-term use.

Oral JAK inhibitors (JAKi) offer patients with atopic dermatitis (AD) a rapid reduction in disease burden and itch, the convenience of oral administration and the ability to dose flexibly. Phase III clinical trials have demonstrated a high efficacy and durability of clinical response with longer-term use of JAKi, although the required laboratory monitoring, boxed warnings and limited follow-up data in AD create challenges when managing this treatment.<sup>1,2</sup> Herein, experts from the International Eczema Council (IEC) have reviewed safety and clinical considerations regarding JAKi class, providing practical guidance for starting and monitoring patients with AD on JAKi.

## Materials and methods

An international group of members of the IEC with expertise in JAKi were invited to participate in writing this article. They ranked topics of interest and were placed into groups covering 10 subsections. For consistency among the authorship subgroups, prior to writing, we obtained current adverse event (AE) data from medical science liaisons from Pfizer (abrocitinib), AbbVie (upadacitinib) and Lilly (baricitinib). These subgroups then performed topic-specific literature reviews, consulted AE and product label data, and provided analysis and expert opinion. The conclusions and recommendations from each subgroup were reviewed and edited by all authors, as well as the IEC Research Committee prior to submission.

## Results

### Clinical indications for use

Oral JAKi are approved in many countries for the treatment of patients with moderate–severe AD. Clinical indications for using JAKi to treat AD varies by region, with some countries endorsing it as a first-line treatment in the absence of risk factors, while others limit its use to a second-line agent after an inadequate response to, or AEs, caused by, conventional oral immunosuppressants or biologics. All JAKi require laboratory monitoring and have boxed warnings

for potential safety issues. Treatment should be initiated through shared decision-making with patients, considering personal risk–benefit assessment, local licensing, monitoring requirements and treatment cost.

### Venous thromboembolism risk

Systemic inflammation from immune-mediated inflammatory disorders (IMiDs) is associated with an elevated risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, due to the creation of a prothrombotic environment.<sup>3</sup> For example, in patients with rheumatoid arthritis (RA), the risk of VTE is 4.7% vs. 2.5% in the general population per 10 000 patient-years (PYs).<sup>4</sup> In contrast, a cohort study of patients aged > 18 years with AD failed to show a link between AD and VTE risk, and an overall low incidence of VTEs in AD.<sup>5</sup>

In 2021, the U.S. Food and Drugs Administration (FDA) updated boxed warnings to include VTE for all JAKi after an FDA-mandated trial for tofacitinib in patients with active RA demonstrated an increased risk of VTEs [despite methotrexate (MTX) use] vs. the tumour necrosis factor (TNF) inhibitor (TNFi) active control arm.<sup>6,7</sup> Study participants were aged ≥ 50 years, had at least one cardiac risk factor and were on concomitant treatment with MTX (> 99.9%) and/or low-dose systemic steroids (57.2%).<sup>6</sup> While increased, the incidence of VTEs remained low and showed a dose-dependent effect of 0.33 events/100 PYs [95% confidence interval (CI) 0.19–0.53] in the tofacitinib 5-mg twice-daily group vs. 0.70 events/100 PYs (95% CI 0.49–0.99) in the 10-mg twice-daily group vs. 0.20 events/100 PYs (95% CI 0.10–0.37) in the TNFi group.<sup>6</sup> In contrast, a meta-analysis that included 42 studies of JAKi in treating IMiDs (inflammatory arthropathies, inflammatory bowel disease, psoriasis) found that the rate of VTEs in the JAKi group was 0.23/100 PYs (95% CI 0.12–0.38) vs. 0.25/100 PYs (95% CI 0.07–0.73) in the placebo group, with no increased risk of VTE in the former (incidence rate ratio 0.68, 95% CI 0.36–1.29).<sup>8</sup> However, this meta-analysis included only phase II and III studies, which often exclude older patients and those with cardiovascular risk factors. It also excluded long-term extension studies, during which most VTE events occur.<sup>9</sup>

JAKi trials in AD demonstrate lower rates of VTE than in RA trials, and these VTEs occurred predominately in patients with pre-existing risk factors and at higher doses. For baricitinib, VTEs were observed in 2 of 2531 patients over 2247 PYs (0.09 events/100 PYs), both at the higher 4-mg dose (in a 51-year-old woman with multiple VTE risk factors and in a 61-year-old man).<sup>10</sup> In abrocitinib trials, VTEs were observed at a rate of 0.3 events/100 PYs (1428 PYs).<sup>11</sup> The VTEs occurred at the higher 200-mg dose and in patients with risk factors, including older age, obesity, recent surgery and a family history of VTE.<sup>11</sup> In upadacitinib trials, the rate of VTEs was <0.1/100 PY. VTEs occurred at both the 15- and 30-mg doses (2788 PYs), although only in patients with a history of VTEs and risk factors.<sup>12</sup> Rates of VTE do not qualitatively appear to be elevated over population-based estimates that range between 0.15 and 0.25 events per 100 PYs in patients aged  $\geq 12$  years with moderate-to-severe AD.<sup>13</sup>

Prior to initiating a JAKi, we recommend consideration of VTE risk factors, including a history of VTE, age > 65 years, a history of inherited thrombophilias (e.g. factor V Leiden), exogenous oestrogen use, recent surgery, immobility, uncontrolled hypertension, obesity, current or prior tobacco use, cancer, pregnancy and concomitant IMiDs.<sup>14</sup> If risk factors are present, consider treatment initiation carefully, on an individual basis, at the lowest dose, engaging patients in shared decision-making and consulting with other specialists if needed (e.g. haematologists). Patients should also be counselled on the warning signs of VTEs and potential VTE risk factors. Additional research is needed to further define the short- and long-term VTE risks for patients with AD.

## Malignancy risk

The risk of malignancy induction by JAKi is an important consideration. While JAK2 inhibitors are used to treat certain myeloproliferative neoplasms, treating IMiDs with JAKi may be associated with lymphoma or solid tumour development.<sup>15–17</sup> Abrocitinib, baricitinib, tofacitinib and upadacitinib all have boxed warnings for an increased risk of malignancy.<sup>17</sup>

Despite the boxed warning, the risk of malignancy is low, as demonstrated by several analyses. A literature search concluded that malignancies in patients with RA occur at similar rates with JAKi and biologic use.<sup>17</sup> A systematic review of JAKi treatment for 8 different indications, including AD, found no increase in malignancy rates over time, including 19 406 PYs of treatment exposure with tofacitinib in randomized controlled trials (RCTs) for RA up to March 2015.<sup>18</sup>

Prospective safety studies showed an increased risk of malignancy with JAKi treatment. The previously mentioned investigation of patients with RA receiving tofacitinib (a pan-JAKi) in a randomized open-label safety endpoint trial resulted in a hazard ratio of 1.48 (95% CI 1.04–2.09) for cancer vs. the TNFi group.<sup>6</sup> Lung cancer was most common with tofacitinib and the incidence rate (IR) of cancer was higher among patients aged  $\geq 65$  years.<sup>6</sup> A randomized study of patients with RA treated with upadacitinib vs. adalimumab found similar malignancy rates [with nonmelanoma skin cancer (NMSC) analysed separately] through to 156 weeks.<sup>17,19</sup> Almost all malignancies were found in patients aged  $\geq 53$  years.<sup>19</sup> Analysis of six double-blinded randomized placebo-controlled studies of baricitinib in AD found that the IR of malignancies (except NMSC) was 0.22/100 PYs vs. 0.66/100 PYs in the placebo-controlled group.<sup>10</sup> The IR of

malignancies excluding NMSC in pooled abrocitinib trials was 0.1/100 PYs.<sup>11</sup> An analysis of six phase IIb/III clinical studies using abrocitinib for moderate-severe AD revealed NMSC IRs of 0.39–0.47 and adjudicated malignancy (prostate cancer, gastric adenocarcinoma; excluding NMSC) IRs of 0.10–0.15.<sup>1</sup> For upadacitinib, the malignancy rate (excluding NMSC) was 0.1/100 PYs at 15 mg and 0.5/100 PYs at the 30-mg dose.<sup>12</sup>

In summary, in clinical trials, malignancies have been found after the initiation of JAKi, especially in older patients. Overall, the risk of malignancies with JAKi remains low, although it cannot be accurately estimated without longer-term observations. Rates do not qualitatively appear to be elevated over population-based estimates that range between 0.30 and 0.36 events per 100 PYs.<sup>20</sup> The contribution to malignancy incidence from JAKi in AD remains unclear.

## Organ dysfunction

Patients with comorbid heart, liver or kidney conditions should be carefully selected for JAKi treatment. Treatment with a JAKi can be associated with increased serum levels of liver enzymes and creatinine.<sup>21</sup> JAKi should not be used for patients with severe hepatic disease (Child–Pugh C), although no dosage adjustment is needed in patients with mild or moderate (Child–Pugh A/B) hepatic impairment.<sup>11,12,22</sup>

Renal function significantly affects JAKi exposure.<sup>21</sup> Baricitinib and abrocitinib are not recommended in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 mL min<sup>-1</sup>] and for patients with mild-to-moderate renal impairment (eGFR  $\geq 30$  mL min<sup>-1</sup>), dose adjustment is recommended according to the package inserts.<sup>11,22</sup> As for upadacitinib, the maximum recommended dosage is 15-mg daily for patients with severe renal impairment (creatinine clearance < 30 mL min<sup>-1</sup>) and no dosage adjustment is advised in patients with mild or moderate renal impairment.<sup>12</sup>

A higher incidence of major adverse cardiac events (MACE; cardiovascular death, myocardial infarction, stroke) was shown in patients with RA treated with tofacitinib vs. a TNFi, resulting in a boxed warning for an increased risk of MACE with oral JAKi.<sup>7,23</sup> MACE occurred at IRs of 0.1 and <0.1 per 100 PYs in clinical trials of upadacitinib 15 and 30 mg, respectively.<sup>12</sup> No MACE occurred during the placebo-controlled period for baricitinib, although one event occurred in the 2-mg group of the extended dataset (IR 0.17 per 100 PYs).<sup>10</sup> In abrocitinib trials for AD the IR for MACE was 0.18 per 100 PYs.<sup>1</sup> Consequently, the benefits and risks of MACE should be discussed with every patient when prescribing JAKi, particularly in patients with cardiovascular risk factors. Previous myocardial infarction or stroke is a relative contraindication for JAKi use.

## Janus kinase inhibitors in pregnancy and lactation

The effects of JAKi on pregnancy have not been extensively studied in humans. Animal studies with doses at many times the standard human dose, found them to be fetidal and teratogenic. Owing to the potential risk of small-molecule JAKi crossing the placenta, all RCTs of JAKi excluded patients not using two highly effective forms of birth control, those planning a pregnancy or those who were already pregnant.

Unplanned pregnancies still occurred in some studies. Most of the available human data are derived from accidental pregnancies during clinical trials and postmarket surveillance safety databases maintained by drug manufacturers.

In AD trials of abrocitinib, seven documented cases of pregnancy resulted in three healthy newborn babies, one healthy ongoing pregnancy, two spontaneous abortions and one unknown outcome.<sup>11</sup> In upadacitinib clinical trials for any indication, 54 reported pregnancies resulted in 17 healthy newborn babies, 12 ongoing pregnancies, 14 spontaneous abortions (10 patients were on concomitant MTX), 9 elective terminations, 1 ectopic pregnancy and 1 unknown outcome.<sup>12</sup> In baricitinib clinical trials and postmarket surveillance, 58 pregnancies resulted in 12 healthy newborn babies, 10 spontaneous abortions, 25 ongoing pregnancies, 5 elective terminations, 3 premature but healthy infants, 2 unknown outcomes and 1 intrauterine loss (this patient was on concomitant MTX).<sup>12,22,24</sup>

Patients who were breastfeeding were excluded from clinical trials, owing to the known excretion of JAKi in animal breast milk. In rats, the concentration of abrocitinib was five times higher in breast milk than in plasma. Owing to the high likelihood – as inferred from animal studies – that JAKi will also be present in human breast milk, the use of JAKi in patients who are lactating is contraindicated. There are currently no published clinical safety data regarding JAKi in patients who are lactating.<sup>11,12</sup>

The impact of JAKi on fertility has not been formally studied in humans. In animal models, abrocitinib had no effect on male spermatogenesis or fertility, but it did have a negative effect on female rat fertility.<sup>11</sup> The negative impact on fertility was reversible 1 month after discontinuation.<sup>11</sup> Upadacitinib did not negatively affect male or female fertility at doses up to 50 and 75 mg kg<sup>-1</sup> daily, respectively.<sup>12</sup> There are no clinical data on the effects of baricitinib on fertility.

Given the lack of conclusive medical evidence on the safety of selective JAKi during pregnancy and the known excretion of JAKi in animal breast milk, we recommend that JAKi be avoided in patients who are trying or planning to become pregnant, if they are pregnant or if they are lactating. Patients who could potentially become pregnant should use highly effective birth control while on treatment and continue birth control for 1 week after stopping baricitinib and 4 weeks after stopping abrocitinib or upadacitinib.<sup>11,12,22</sup>

## Janus kinase inhibitors and infections

JAK1/2 inhibition affects cellular cytotoxicity by blocking interferon- $\gamma$  signalling, inhibiting cellular killing via extracellular apoptosis, necroptosis and pyroptosis.<sup>25–27</sup> Thus, fighting infectious agents such as viruses or intracellular bacteria can be impaired.<sup>28</sup>

Herpes zoster (HZ) is an established complication of JAKi, and emerging long-term safety data will clarify the magnitude of risk among the selective JAKi used in AD. People with AD treated with abrocitinib and upadacitinib have, in head-to-head studies, shown higher rates of HZ infection than those on dupilumab treatment.<sup>29–33</sup> The prevalence of HZ infections in people with AD was <3% on oral JAKi, and most cases were mild or moderate.<sup>34</sup> Rates of eczema herpeticum (EH) appear to increase dose-dependently in people with AD on baricitinib.<sup>10</sup> Higher IRs of EH have also been found in abrocitinib trials (when compared with placebo) and in upadacitinib

trials (when compared with dupilumab) but not in a dose-dependent manner and the overall rates were low.<sup>1,29</sup>

Tuberculosis (TB) was a concern, owing to the potential vulnerability to *Mycobacterium tuberculosis* infection with JAKi treatment.<sup>30,31</sup> In people with AD, reports of TB in patients on baricitinib, abrocitinib or upadacitinib were absent or scarce.<sup>1,10,29</sup> Rare opportunistic infections have been reported in oral JAKi trials for AD but not at elevated rates compared with placebo.<sup>10–12</sup>

Vaccination is an important tool for infection prevention in patients on JAKi (Table 1). Inactivated pneumococcal, influenza and a two-dose Shingrix series can be considered for patients aged > 18 years.<sup>30</sup> If the inactivated recombinant zoster vaccine is not available, the live zoster vaccine (Zostavax) should be administered at least 3–4 weeks before initiating JAKi.<sup>30</sup> Ideally, these vaccines series should be completed prior to JAKi initiation; however, certain clinical scenarios make treatment delays challenging. Further studies are needed to assess the optimal duration off JAKi treatment needed to mount protective immune responses from vaccination.

The European Task Force on Atopic Dermatitis recommends a 1-week pause of JAKi treatment after a COVID-19 vaccination, to prevent an insufficient vaccination response. However, it also suggests following guidelines and decisions issued by local and national health authorities in each country.<sup>35</sup> Nonlive COVID-19 vaccines with higher efficacies should be the first choice.<sup>36</sup>

## Adverse events

### Gastrointestinal

Abdominal pain, diarrhoea, nausea and vomiting have been reported with oral JAKi use. In JAKi safety studies in RA, nausea was reported by 3–7% of patients, while in AD studies, the frequency of nausea was as high as 7–20%.<sup>2,37–39</sup> Nausea and vomiting were most often observed with abrocitinib, in particular in adolescents, and were dependent on the JAKi dosage.<sup>2,33,40–42</sup> Most cases of nausea occurred in women within the first week of treatment and resolved after a median of 15 days.<sup>1</sup> Gastrointestinal perforation has been reported in patients with RA on JAKi but not – to date – in people with AD.<sup>10,43</sup>

### Acne

Acne and folliculitis have been uncommonly reported in RA clinical trials but have been recorded among the most common cutaneous AEs in AD trials.<sup>2,41,44,45</sup> JAKi-related acne in people with AD presented classically in distribution and morphology, with comedonal and inflammatory lesions involving the face, upper chest and back.<sup>46</sup> In JAKi clinical trials for AD, acne rates were lowest for baricitinib and highest for upadacitinib, with a clear dose-dependent trend. Up to 17% of patients taking the highest daily dose of upadacitinib (30 mg) were affected.<sup>44,46</sup> Patients who develop acne generally respond well to common acne treatments.

### Headache

Headache has been reported as the most common nervous system-related AEs for all JAKi in both RA and AD.<sup>34,41,45</sup> In people with AD, headache severity was generally mild and brief (median duration < 1 day), affecting up to 10% of patients.<sup>34,47</sup>



## Laboratory and clinical monitoring

In JAKi clinical trials, observed laboratory changes included increases in creatinine phosphokinase (CPK), lipids and liver enzymes, and decreases in blood cell parameters. Some effects were associated with all JAKi, whereas others were only reported with specific JAKi use. Based on published data and product monographs, we propose a general strategy to monitor laboratory parameters when using JAKi to treat AD. However, before starting JAKi, it is important to consult the country- and medication-specific product monograph, as recommended laboratory monitoring may vary and should take precedence. Detailed analysis of differences between individual JAKi with regard to each laboratory parameter is beyond the scope of this article.

Prior to starting treatment, a thorough medication list review is advised, as several drug interactions can occur with JAKi. Ideally, screening for TB, hepatitis B virus, hepatitis C virus and HIV should be performed before treatment initiation. A pregnancy test is recommended for those who have the potential to become pregnant, depending on their sexual activity and contraception status. With regard to laboratory monitoring, we suggest measurement of a baseline complete blood count (CBC) with differential, complete metabolic panel (glucose, sodium, potassium, bicarbonate, chloride, calcium, albumin, total protein, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bilirubin, blood urea nitrogen and creatinine) and lipid panel. CBC, liver enzymes and lipids should be rechecked between 4 and 12 weeks after initiation and every 3–6 months thereafter according to product monographs, patient characteristics and risk assessment (Table 1). JAKi product monographs for laboratory monitoring have minor variations and should be reviewed.

### Haematological parameters

Consider treatment interruption and dose adjustment if a patient's haemoglobin decreases below 8 g dL<sup>-1</sup> (5 mmol L<sup>-1</sup>), and their absolute lymphocyte count is <0.5 × 10<sup>9</sup> cells L<sup>-1</sup> or their absolute neutrophil count is <1 × 10<sup>9</sup> cells L<sup>-1</sup>. Rare cases of thrombocytopenia have been reported, mostly within a few weeks of starting abrocitinib. Abrocitinib is not

recommended in patients with a platelet count <150 × 10<sup>9</sup> cells L<sup>-1</sup> and should be stopped if a person's platelet count falls below 50 × 10<sup>9</sup> cells L<sup>-1</sup>. JAKi treatment can sometimes be reinitiated at a lower dose without recurrence of thrombocytopenia.

### Liver enzymes

Increases in liver enzymes have been reported with some JAKi, particularly upadacitinib. In cases of liver enzyme increases, we advise evaluating for the presence of a previously unknown liver disease or potential cases of drug-induced liver injury. If drug-induced liver injury is suspected or liver enzymes are persistently elevated, treatment should be interrupted and referral to gastroenterology should be considered.

### Lipids

JAKi have been reported to increase total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. As the clinical impact of these changes is unknown, consider measuring lipid levels at the frequencies described in Table 1 and treating lipid increases according to national guidelines.

### Renal function

JAKi are mostly metabolized by cytochrome P450 enzymes and metabolites excreted partly in urine. Limited studies have been conducted in patients with moderate-to-severe renal impairment, and elevated JAKi levels were reported in these patients. We recommend measuring renal function at baseline and periodically during treatment, depending on the clinical situation (e.g. a patient with renal impairment) (Table 1). If signs of renal dysfunction are present, we recommend considering closer follow-up laboratory monitoring, stopping treatment and a potential referral to nephrology.

### Creatinine phosphokinase

Elevated CPK levels have been frequently reported during JAKi treatment. These increases are usually asymptomatic and commonly associated with physical exercise. In general, monitoring CPK levels during treatment with JAKi is not recommended. In case of clinical symptoms (e.g. muscle weakness and/or myalgia), CPK levels should be measured.

**Table 1** Laboratory and vaccine monitoring recommendations for Janus kinase inhibitor treatment of atopic dermatitis

	Pretreatment	4–12 weeks after initiation <sup>a</sup>	Every 3–6 months
TB screening <sup>b</sup>	×		
Pregnancy <sup>c</sup>	×	×	×
HBV <sup>d</sup> /HCV	×		
HIV <sup>e</sup>	×		
CBC with differential	×	×	×
CMP	×	×	×
HDL cholesterol, LDL-cholesterol, TG	×	×	Annually
Vaccination	Comments		
Inactivated pneumococcal vaccine	Recommended for patients aged > 18 years		
Influenza	Recommended annually		
Shingrix – recombinant zoster vaccine	Recommended for patients aged > 18 years; two doses separated by 2–6 months		

CBC, complete blood count; CMP, complete metabolic panel; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TB, tuberculosis; TG, triglycerides. <sup>a</sup>Laboratory monitoring recommendations differ by product monograph – consult product monograph for specific recommendations. <sup>b</sup>Depending on local guidelines: may include risk assessment (questionnaire), chest X-ray, interferon-γ release assay/Mantoux (purified protein derivative) test. <sup>c</sup>Depending on potential to become pregnant, sexual activity and contraception use. <sup>d</sup>Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody. <sup>e</sup>In case of risk factors.

## Long-term use

### *Dose flexibility*

Upon achieving disease control, we recommend patients are put on the lowest dose required to maximize clinical efficacy and minimize the risk of AEs. As small molecules, JAKi do not confer the same risk of antidrug antibody formation as biologics. Therefore, breaks in treatment may be feasible without risking future loss of efficacy. When a patient is on the lowest effective dose for maintenance, the patient may be empowered with on-demand dose adjustments when needed, given the rapid response to these medications. This approach may not be feasible in clinical settings with more restrictive drug refill processes. Ideally, dose flexibility should facilitate optimal disease control in patients with variable disease courses and reduce cumulative medication exposure.

### *Risk minimization*

Certain considerations should be given to minimize the long-term risk of JAKi use. JAKi should be used cautiously in patients aged >65 years. Ideally, providers should encourage healthy lifestyle choices, including maintaining an ideal bodyweight and stopping smoking (if applicable). If feasible, vaccinations should be current before starting a JAKi. For patients who experience recurrent herpes simplex virus or HZ outbreaks, prophylactic antiherpetic treatment may be needed. When possible, other medications that increase risk of malignancy, VTE or haematological anomalies should be avoided. Combination treatments for patients may be required; however, safety data only exist for MTX, topical corticosteroids and topical calcineurin inhibitors.<sup>42,43</sup>

## Discussion

The efficacy of JAKi has been well established in short- and intermediate-length studies (up to 2 years), while ongoing long-term studies will provide information on the durability and safety with continuous use.<sup>48,49</sup> Episodic use and dose alterations also need further study – for example, the potential for episodic use of JAKi to replace corticosteroids for AD flares and assessing for any long-term consequences from variable JAKi dosing for managing chronic AD.

The efficacy and safety of JAKi vs. interleukin (IL)-4/IL-13 antagonists has been studied in the short-term, but longer, randomized studies are needed. The potential use of oral JAKi in combination with medications such as MTX or IL-4/IL-13 or IL-13 antagonists also warrants further research.

Currently, no JAKi is approved in any country for children aged <12 years, although studies in which children aged as young as 3 years are ongoing. Future research will need to define the safety and impact on immunological development and comorbidities. Establishing the impact of JAK blockade on classic AD comorbidities such as asthma and allergic rhinitis is another key area that requires further study. The signalling of type 2 cytokines involved in AD pathogenesis and atopic comorbidities is downregulated by JAKi. Thus, JAKi may modify AD comorbidities.

A final, critical piece of the jigsaw regarding the future of JAKi for AD treatment is to further establish their safety profile over several years of chronic continuous use.

Unfortunately, long-term studies of tofacitinib in people with RA were generalized to the entire field of JAKi safety. Tofacitinib is a pan-JAKi, unlike upadacitinib and abrocitinib, which both predominantly block JAK1; baricitinib, by contrast, blocks JAK1 and JAK2. These mechanistic differences may translate into different, possibly safer, long-term AE profiles than with tofacitinib. Real-world data will be critical in establishing the long-term safety of JAKi as monotherapy or in combination with other systemic treatments.

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## Conflicts of interest

A.A. has institutional grants with AbbVie, Amgen, Amgen, Arcutis, Bristol-Myers Squibb, Cara Therapeutics, Castle, Dermavant, Galderma, LEO Pharma, Novartis, Valeant (Bausch Health) and Vyne; is an advisory board member or consultant with Pfizer, AbbVie, Allergan, Amgen, Almirall, Alphyn, Amgen, Apogee, Arcutis, Bausch Health, Beiersdorf, Bristol-Myers Squibb, Cara Therapeutics, Canfield, Castle, Cutera, Dermavant, Eli Lilly, EPI Health, Galderma, Incyte, Janssen, LEO Pharma, L'Oréal, Ortho, Sanofi Regeneron, Swiss-American, UCB, VisualDx and Vyne; and has given lectures and presentations for Pfizer, Bristol-Myers Squibb, Regeneron and Sanofi Genzyme. V.A. has clinical trials with Sanofi, Eli Lilly and Amgen, and has consulted for AbbVie and Pfizer. R.B. is an advisory board member, consultant, speaker and/or investigator for and receives honoraria and/or grants from AbbVie, Amgen, Apogee, Arcutis, Asana BioSciences, Bellus, BioMimetix, Bluefin, Biomedicine, Boehringer Ingelheim, Boston Pharma, CARA Therapeutic, Dermavant, Eli Lilly, Escient, Evidera, Fresh Tracks (Brickell), Galderma, GlaxoSmithKline, Incyte, Inmagene Bio, Janssen, LEO Pharma, Merck, Novartis, Opsidio, Pfizer, RAPT Therapeutic, Sanofi, Target RWE, Vyne Therapeutics and Zencor. R.B. is also an employee and shareholder of Innovaderm Research. A.B. has served as a speaker (received honoraria) for Eli Lilly, Pfizer and UCB; has served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Amgen, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis, Arena, ASLAN, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO Pharma, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome and Xencor; and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Amgen, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, DermBiont, Eli Lilly, Evelo, Evommune, Galderma, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma and Ventyx. R.C. has served as an advisor, consultant,

speaker and/or investigator for AbbVie, Amgen, Apogee Therapeutics, Arcutis, Argenx, ASLAN Pharmaceuticals, Beiersdorf, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Dermavant, Eli Lilly, FIDE, Galderma, Genentech, GSK, Incyte, LEO Pharma, L'Oréal, Nektar Therapeutics, Opsidio, Pfizer, Regeneron, RAPT, Sanofi and UCB. M.J.C. has grants from Hyphens Pharma, Johnson & Johnson, Kymab, LEO Pharma, L'Oréal, Perrigo, Pfizer, Regeneron Pharmaceuticals and Sanofi; and has received personal fees from AbbVie, Astellas Pharma, Boots, Dermavant, Eli Lilly, Galapagos, Galderma, Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Perrigo, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron Pharmaceuticals and Sanofi. S.G.D. has grants with Sanofi, Almirall, Johnson & Johnson and LEO Pharma; and has received grants and personal fees from Perrigo, Pfizer and Hyphens Pharma. L.F.E. has served as a consultant, speaker, advisory board member or investigator for AbbVie, Amgen, Apogee, Arcutis, ASLAN, Bristol-Myers Squibb, Castle Biosciences, Dermavant, Eli Lilly, Forte, Galderma, Incyte, Janssen, Johnson & Johnson, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Target RWE and UCB. K.E. has served as a consultant and/or scientific advisor for AbbVie, Almirall, Bristol-Myers Squibb, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and UCB; and has received research support from AbbVie, LEO Pharma, Lilly, Janssen and UCB. M.G. has served as an investigator, speaker and/or adviser for AbbVie, Amgen, Akros, Arcutis, Aristeia, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Celgene, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Meiji, Merck, MoonLake, Nimbus, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union and Ventyx. E.G.-Y. has research grants from Boehringer Ingelheim, LEO Pharma, Pfizer, Cara Therapeutics, UCB, Kyowa Kirin, RAPT, Amgen, GSK, Incyte, Sanofi, Bristol-Meyers Squibb, ASLAN, Regeneron, AnaptysBio, Concert and Janssen; and has been a consultant for AbbVie, Almirall, Amgen, AnaptysBio, Apogee Therapeutics, Apollo Therapeutics, Artax Biopharma, AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Cara Therapeutics, Centrexion Therapeutics, Connect Biopharm, Eli Lilly, Enveda Biosciences, Escient Pharmaceuticals, Fairmount Funds Management, Galderma, Gate Bio, Google Ventures (GV), GSK Immunology, Horizon Therapeutics USA, Incyte, Inmagene, Janssen Biotech, Japan Tobacco, Jasper Therapeutics, Kyowa Kirin, LEO Pharma, Merck, Nektar Therapeutics, Novartis Pharmaceuticals, NUMAB Therapeutics, OrbiMed Advisors, OTSUKA Pfizer, Pharmaxis, Pioneering Medicine VII, Proteologix US, RAPT, Regeneron Pharmaceuticals, Ribon Therapeutics, Sanofi, SATO, Schrödinger, Sun Pharma Advanced Research Company (SPARC), Teva Branded Pharmaceutical Products R&D and UCB. D.-J.H. is or has been a consultant and/or investigator for AbbVie, Almirall, AstraZeneca, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and UCB. A.D.I. has received consulting fees from AbbVie, Almirall, Arena, Benevolent AI, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron and Sanofi; has patents pending with Johnson & Johnson and Regeneron; and is President Elect of the International Eczema

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VeriSkin. S.S. has grants from Almirall, Beiersdorf, LEO Pharma, Galderma and Sanofi; has consulted for and been on advisory boards for AbbVie, Almirall, Beiersdorf, Clexio, Escient, Galderma, Grünenthal, Incyte, Integrity CE, Kiniksa, Klinge Pharma, Lilly, P.G. Unna Academy, Pfizer, Sanofi, touchIME, Vifor and WebMD; and has delivered lectures and presentations for AbbVie, BMS, FOMF, Galderma, LEO Pharma, L'Oréal, MEDahead, Morosscience, Novartis, Sanofi, P. G. Unna Academy, Pfizer, UCB and Vifor. J.P.T. reports, with no relation to the present manuscript, that he has previously been an advisor for AbbVie, Almirall, Arena Pharmaceuticals, OM Pharma, ASLAN Pharmaceuticals, Union Therapeutics, Eli Lilly, LEO Pharma, Pfizer, Regeneron and Sanofi Genzyme; has been a speaker for AbbVie, Almirall, Eli Lilly, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme; and has received research grants from Pfizer, Regeneron and Sanofi Genzyme. He is currently an employee of LEO Pharma. J.Y. has served on advisory boards for Sanofi, Incyte and Arcutis; has served as a consultant for the National Eczema Association, iRhythm, O'Glancee and Inner Archways; and has served as site investigator on clinical trials sponsored by AbbVie, Pfizer, Lilly and SmartPractice. C.H., A.A.L., J.I.O., Y.R.-Y., N.S. and G.T. declare no conflicts of interest.

## Data availability

The data underlying this article are available in the article.

## Ethics statement

Not applicable.

## Patient consent

Not applicable.

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